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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,787	01/10/2002	Chong-Sheng Yuan	466992000221	9117

25225 7590 02/10/2004

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/043,787	YUAN, CHONG-SHENG	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *36-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12/30/02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-50 are pending.

Applicant's election without traverse of Group XV, claims 1-35 drawn in part to a method for assaying homocysteine, S-adenosylhomocysteine or adenosine with a mutant SAH hydrolase which comprises the amino acid sequence of SEQ ID NO: 1 and the mutation T158Y, in a communication filed on 11/28/2003 is acknowledged.

It is noted that while Applicants refer to an election of species in page 3 of the response filed on 11/28/2003, the restriction requirement mailed on 7/25/2003 was not an election of species. The Examiner, according to the criteria set forth in MPEP 803 for restriction of patentably distinct inventions, indicated why the inventions are independent or distinct and why the search of all inventions would impose a serious burden on the Office (pages 4-5).

Claims 36-50 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

1. The specification is objected to since the reference to prior applications indicated in the first paragraph of the specification does not contain the current status of all nonprovisional parent applications to which priority is claimed. See particularly, U.S. Application No. 09/347878 and 09/454205. Appropriate correction is required (MPEP 201.11).

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. It is suggested that the term "compositions" be deleted since the elected claims are directed to a method.

3. The specification is objected to for the following reasons. In Example 4, page 44, Step 1 and page 46, Step 1, the specification describes the formation of SAH from Hcy but it does not include the addition of Ado, which is required for the formation of SAH (i.e. Hcy + Ado → SAH). It is noted that Step 2 requires the removal of Ado. Clarification is required.

Priority

4. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/301,895 filed on 06/29/2001.

5. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/457,205 filed on 12/06/1999, and 09/347,878 filed on 07/06/1999.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on 12/30/2002 is acknowledged. Reference No. 65 has not been considered since there is no author's name associated with it. Reference No. 128 has not been considered since its publication date is missing. The remaining references in the submission are in compliance with the provisions of 37 CFR 1.97 and are being considered by the examiner.

Drawings

7. The drawings filed on 1/10/2002 are accepted by the Examiner.

Claim Objections

8. Claim 7 is objected to since it is partially drawn to non-elected inventions. Examination of claim 7 will be restricted to the subject matter elected, which in the instant case is a method for assaying homocysteine, S-adenosylhomocysteine, or adenosine with a mutant SAH hydrolase, wherein said

hydrolase comprises the amino acid sequence set forth in SEQ ID NO: 1 except that the threonine residue at position 158 has been substituted with a tyrosine residue. Appropriate correction is required.

9. Claim 1 is objected to due to the recitation of "and said binding affinity and/or said attenuated...". For clarity, it is suggested that the term be replaced with "and wherein said binding affinity and/or said attenuated..". Appropriate correction is required.

10. Claim 1 is objected to due to the recitation of "SAH or adenosine, or a combination thereof". For clarity, it is suggested that the term be replaced with "SAH, adenosine, or a combination thereof". Appropriate correction is required.

11. Claims 18-22, 28, and 29 are objected to due the recitation of "SAH or a derivative or an analogue thereof". For clarity, it is suggested that the term be replaced with "SAH, SAH derivative or SAH analogue" or similar. Appropriate correction is required.

12. Claim 20 is objected to due to the recitation of "labeled SAH is fluorescin-SAH conjugate or Rocamin-SAH conjugate". For clarity, it is suggested that the term be replaced with "labeled SAH is a fluorescin-SAH conjugate or a Rocamin-SAH conjugate". Appropriate correction is required.

13. Claims 20, 21 and 22 are objected to due the recitation of "linker of 1-15 carbon atom length". For clarity, it is suggested that the term be replaced with "1-15 carbon atom linker" or "linker of 1-15 carbon atoms in length. Appropriate correction is required.

14. Claim 21 is objected to due the recitation of "derivative is glucose-6-phosphate dehydrogenase...". For clarity, it is suggested that the term be amended to recite "derivative is a glucose glucose-6-phosphate dehydrogenase..". Appropriate correction is required.

15. Claim 22 is objected to due to the recitation of "derivative is bovine albumin-SAH conjugate". For clarity, it is suggested that the term be amended to recite "derivative is a bovine albumin-SAH conjugate". Appropriate correction is required.

16. Claim 26 is objected to due to the recitation of "horse radish". It is suggested that the term be replaced with "horseradish". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

19. Claims 1 and 2 (claims 3-35 dependent thereon) are indefinite in the recitation of "catalytic activity" for the following reasons. It is unclear from the recitation of the term, which activity is being referred to. According to the specification, SAH hydrolase can have several catalytic activities, e.g. 3'-oxidative activity, 5'-hydrolytic activity, and 3' reduction activity (page 12, lines 26-27). Therefore, one cannot reasonably determine which catalytic activity is being referred to in the claims. For examination purposes, it will be assumed that the term refers to "3'-oxidative activity, 5'-hydrolytic activity, and 3' reduction activity". Correction is required.

20. Claim 2 is indefinite in the recitation of "amino acid residue that is directly involved in the SAH hydrolase's catalytic activity" for the following reasons. As written, it is unclear which amino acid is being referred to since the term "directly involved" as it relates to catalytic activity has not been defined in the claim or the specification. One cannot determine if the term refers to an amino acid which is essential for the activity recited such that its absence results in lack of activity, or if it is an amino acid whose absence may reduce or increase the desired activity. For examination purposes, both interpretations, i.e. (1) amino acid which is essential for the activity recited, and (2) amino acid whose absence may reduce or increase the desired activity, will be used. Correction is required.

21. Claims 10 and 11 (claim 12 dependent thereon) are indefinite in the recitation of "access adenosine" as it is unclear what the meaning of the term "access adenosine" is. For examination purposes, it will be assumed that the intended meaning is "excess adenosine". Correction is required.

22. Claim 12 is indefinite in the recitation of "wherein the wild-type SAH hydrolase inhibitor is..." since the term "SAH hydrolase inhibitor" lacks antecedent basis. For examination purposes, it will be assumed that the term recites "wherein the wild-type SAH hydrolase is inhibited by .....". Correction is required.

23. Claim 13 (claims 14-15 dependent thereon) is indefinite in the recitation of "further comprising the step of removing the reducing agent used to convert oxidized or conjugated..." since there is no antecedent basis for the "reducing agent". For examination purposes, it will be assumed that the term recites "wherein a reducing agent is used to convert oxidized or conjugated....and wherein said agent is removed prior to or concurrently with...". Correction is required.

24. Claim 18 (claims 19-22, 27-29 dependent thereon) is indefinite in the recitation of "presence of a labeled SAH, or a derivative or an analogue thereof, thereby the amount of the mutant SAH hydrolase bound to the labeled SAH inversely relates to the amount of ...." for the following reasons. First, it is unclear as to how the amount of the mutant SAH hydrolase bound to the labeled SAH can be estimated if it appears from the specification (Example 4, step 6) that the amount to be estimated is the amount of labeled SAH bound to the mutant SAH hydrolase. In addition, it is noted that while the claim refers to a labeled SAH, a derivative or an analogue thereof, there is no indication as to how the labeled SAH derivative or labeled SAH analogue are used in the method of claim 18. There is only mention of how the labeled SAH is used to estimate SAH in the sample. For examination purposes, it will be assumed that the claim recites "the method of claim 1 wherein the SAH is contacted with the mutant SAH hydrolase in the presence of a labeled SAH, an SAH derivative, or an SAH analogue, thereby the amount

of labeled SAH, SAH derivative, or SAH analogue inversely relates to the amount of SAH in the sample". Correction is required.

25. Claims 19-22, 24, 28, 29 (claims 25-27 dependent thereon) are indefinite in the recitation of "fluorescently, enzymatically or proteinaceously labeled" for the following reasons. The term "fluorescently labeled" indicates that SAH/SAH hydrolase has been labeled using a fluorescence method to attach the label to SAH/SAH hydrolase. The term "enzymatically labeled" indicates that the analogue has been labeled using an enzyme to attach the label to SAH/SAH hydrolase. The term "proteinaceously labeled" indicates that the analogue has been labeled using a protein to attach the label to SAH/SAH hydrolase. It is noted however that one of skill in the art would conclude that the method can be practiced with SAH/SAH hydrolase that has been labeled with a fluorophore, an enzyme or a protein tag. If the latter is the intended meaning of the term, it is suggested that the claim be amended to recite "fluorophore labeled", "enzyme labeled", or "protein labeled". For examination purposes, the suggested language will be used. Correction is required.

26. Claim 20 is indefinite in the recitation of "wherein the ....labeled SAH is fluorescin-SAH conjugate or Rocamin-SAH conjugate, said fluorescin or Rocamin being linked to said SAH or a derivative or an analogue thereof by a linker..." for the following reasons. While the claim further limits the labeled SAH to be either a fluorescin-SAH or a Rocamin-SAH conjugate, there is no antecedent basis for fluorescin or Rocamin as it relates to a derivative of SAH or an analogue thereof. For examination purposes, it will be assumed that the claim is directed to the method of claim 19 (as interpreted above) wherein said SAH, SAH derivative, or analogue thereof is labeled with fluorescin or Rocamin, and wherein said fluorescin or Rocamin is linked to said SAH, SAH derivative, or SAH analogue by a 1-15 carbon atom linker. Correction is required.

27. Claim 21 is indefinite in the recitation of "wherein the... labeled SAH derivative is ....., said G-6-PDH, alkaline phosphatase, or malate dehydrogenase being linked to said SAH or a derivative or an

analogue thereof ....." for the following reasons. While the claim further limits the labeled SAH derivative, there is no antecedent basis for G-6-PDH, alkaline phosphatase, or malate dehydrogenase as it relates to SAH or an analogue thereof. For examination purposes, it will be assumed that the claim is directed to the method of claim 19 wherein said SAH, SAH derivative, or SAH analogue is labeled with G-6-PDH, alkaline phosphatase, or malate dehydrogenase, and wherein said G-6-PDH, alkaline phosphatase, or malate dehydrogenase is linked to said SAH, SAH derivative or SAH analogue by a 1-15 carbon atom linker. Correction is required.

28. Claim 22 (claim 27 dependent thereon) is indefinite in the recitation of "wherein the proteinaceously labeled SAH derivative is bovine albumin-SAH conjugate, said bovine albumin being linked to said SAH or a derivative ...." for the following reasons. While the claim further limits the labeled SAH derivative, there is no antecedent basis for bovine albumin as it relates to SAH or its analogue. For examination purposes, it will be assumed that the claim is directed to the method of claim 19 wherein said SAH, SAH derivative, or analogue thereof is labeled with bovine albumin, and wherein said bovine albumin is linked to said SAH, SAH derivative, or SAH analogue by a 1-15 carbon atom linker. Correction is required.

29. Claims 28 and 29 are indefinite in the recitation of "resulting change of ... is measured for assessing Hcy, SAH or adenosine" as it is unclear which property of Hcy, SAH or adenosine is being assessed. For examination purposes, it will be assumed that the term's intended meaning is "resulting change of ....is measured for assessing the presence or amount of Hcy, SAH or adenosine in the sample". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

30. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

31. Claims 1-6 and 8-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 8-17, 23-26, 30-34 are directed to a method for assaying homocysteine (Hcy), S-adenosylhomocysteine (SAH) or adenosine in a sample with a genus of mutant SAH hydrolases, wherein said mutant SAH hydrolases have binding affinity for Hcy, SAH or adenosine but have attenuated 3'-oxidative activity, 5'-hydrolytic activity, and 3' reduction activity, and wherein said attenuated activities are caused by a mutation in the hydrolases' catalytic sites, binding sites for NAD, NADH, Hcy, SAH, adenosine, or a combination of mutations as indicated above. Claim 2 is directed to the method of claim 1 wherein the mutations are at any residue (1) which is essential for 3'-oxidative activity, 5'-hydrolytic activity, and 3' reduction activity, or essential for binding with NADH, NAD, Hcy, SAH, or adenosine, (2) whose absence may reduce or increase 3'-oxidative activity, 5'-hydrolytic activity, and 3' reduction activity, or may reduce or increase binding with NADH, NAD, Hcy, SAH, or adenosine, or (3) adjacent to any of the residues of (1) or (2). Claim 3 is directed to the method of claim 1 with the added limitation that the mutant SAH hydrolases have enhanced binding affinity for Hcy, SAH or adenosine when compared to the wild-type SAH hydrolases from which these hydrolases derive. Claim 4 is directed to the method of claim 1 wherein the mutant SAH hydrolases have at least 50 fold higher binding affinity for Hcy, SAH or adenosine when compared to the wild type SAH hydrolases from which they derive. Claims 5-6 are directed to the method of claim 1 wherein the mutant SAH hydrolases are derived from a genus of mammalian or human SAH hydrolases. Claims 18-22, 27-29 are directed to the method of claim 1 wherein SAH is contacted with the genus of mutant SAH hydrolases in the presence of a labeled SAH, a

genus of labeled SAH derivatives or a genus of labeled SAH analogues such that the amounts of labeled SAH, labeled SAH derivatives or labeled SAH analogues bound to the mutant SAH hydrolases inversely relate to the amount of SAH in the sample. Claim 35 is directed to the method of claim 1 further comprising detecting cholesterol and/or folic acid in the sample.

The written description requirement for a genus of compounds required to practice a claimed method may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus of compounds required to practice the claimed method. In the instant case, while the specification discloses (1) a method for assaying Hcy, SAH, or adenosine with a mutant SAH hydrolase, wherein said hydrolase comprises the amino acid sequence set forth in SEQ ID NO: 1 and also comprises a substitution at position 302 wherein a phenylalanine has been substituted with a serine (F302S), (2) several mutant hydrolases which comprise the amino acid sequence of SEQ ID NO: 1 and substitutions/deletions at several positions, as indicated in the first column of Table 1, (3) nucleic acids known in the art to encode SAH hydrolases which Applicants assert can be used in obtaining polynucleotides encoding SAH hydrolases (page 18, first paragraph, page 19, line 3), (4) mutants of the human SAH hydrolase of SEQ ID NO: 1 which have higher binding affinity for SAH (Figure 5), and (5) detection of Hcy concentration by using fluorophore labeled Ado-Cys or Ado-5'ester, the specification fails to disclose (a) all other wild-type SAH hydrolases from which mutant SAH hydrolases having the functional characteristics recited in the claims can be made, (b) which mutations in these unknown wild-type SAH hydrolases can be made such that their variants (mutants) display the desired characteristics, (c) the critical structural elements in any polypeptide which are characteristic of any SAH hydrolase, (d) which are the amino acids in any SAH

hydrolase that can be substituted, deleted or inserted such that the resulting mutant SAH hydrolases have at least 50 fold increase in binding affinity for Hcy, SAH or adenosine, (e) SAH derivatives or SAH analogs which can be used in the claimed method such that the amount of SAH in a sample can be estimated, or (f) the compounds/directions required for the detection of cholesterol or folic acid after assaying for Hcy, SAH or adenosine in any sample which has been treated such that a mutant SAH hydrolase can be used for the determination of the presence or amounts of Hcy, SAH or adenosine.

The argument can be made that the recited genus of wild-type and mutant SAH hydrolases is adequately described by the polypeptide of SEQ ID NO: 1 and the disclosed variants of such polypeptide, since one could use structural homology using the structure of SEQ ID NO: 1 and its variants as disclosed in the specification as well as those known in the art to isolate other mutant SAH hydrolases as required by the claimed method. However, it is noted that the art teaches the unpredictability of using structural homology to accurately determine function and even a high degree of structural homology may not result in functional homology. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. In view of the absence of any information correlating structure with the desired functional characteristics, such that one may predict all the members of the genus of compounds recited by the claims, and the disclosure of a few species of compounds which are not representative of all attributes and species within the genera required to practice the claimed invention, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

32. Claims 1-6 and 8-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for assaying Hcy, SAH, or adenosine with a mutant SAH hydrolase, wherein said SAH hydrolase comprises the amino acid sequence set forth in SEQ ID NO: 1 and also comprises the substitutions at those positions recited in claim 7 and those positions disclosed in the specification, wherein said mutant SAH hydrolase has attenuated 3'-oxidative activity, 5'-hydrolytic activity, and/or 3' reduction activity, and the same, or higher, binding affinity for Hcy, SAH or adenosine when compared to the polypeptide of SEQ ID NO: 1, wherein the mutant SAH hydrolase can be labeled and wherein a labeled Ado-Cys or Ado-5'ester can be used, does not reasonably provide enablement for (1) a method for assaying Hcy, SAH, or adenosine using any mutant SAH hydrolase having the functional characteristics recited in the claims, (2) the method of (1) further using any labeled SAH derivative or SAH analog, (3) the method of (1) or (2) further comprising detecting cholesterol and/or folic acid in the sample by any means, or (4) the method of (1) further comprising detecting cholesterol and/or folic acid in a sample by any means, wherein the mutant SAH hydrolase comprises SEQ ID NO: 1 and also comprises the amino acid substitutions recited in claim 7 or in the specification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims as described above, is not commensurate with the enablement provided in view of the large number of unknown wild-type SAH hydrolases, unknown mutations in any wild-type

SAH hydrolase which would result in the recited functional characteristics, extremely large number of unknown SAH derivatives and SAH analogs, and unknown methods to detect cholesterol and folic acid in a sample which has been treated to interact with a mutant SAH hydrolase for determining presence or amounts of Hcy, SAH or adenosine, required to practice the claimed method. As indicated above, while the specification is enabling for a method for assaying Hcy, SAH, or adenosine with a mutant SAH hydrolase, wherein said SAH hydrolase comprises the amino acid sequence set forth in SEQ ID NO: 1 and the substitutions at those positions recited in claim 7 as well as those positions disclosed in the specification, wherein said mutant SAH hydrolase has attenuated 3'-oxidative activity, 5'-hydrolytic activity, and/or 3' reduction activity, wherein the mutant SAH hydrolase has the same, or higher, binding affinity for Hcy, SAH or adenosine when compared to the polypeptide of SEQ ID NO: 1, wherein the mutant SAH hydrolase can be labeled, and wherein a labeled Ado-Cys or Ado-5'ester can be used, the specification fails to disclose other wild type SAH hydrolases which can be mutated to display the recited characteristics, amino acids in any wild-type hydrolase which can be modified to obtain the desired characteristics, SAH derivatives or SAH analogs which can be used in the method as recited, or how to assay for cholesterol or folic acid after assaying for Hcy, SAH or adenosine as required in the claimed method. In addition, the art as discussed above, teaches the unpredictability of isolating proteins of similar function based solely on structural homology and indicates that even high structural homology does not always results in functional homology. Since structure determines function, one of skill in the art would require some knowledge or guidance as to which are the structural elements in any wild type SAH hydrolase which correlate with the functional characteristics desired. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to display the desired function, and the unpredictability of the prior art in regard to isolation of functional homologs based solely on structural homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the full scope of the

claimed method. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Double Patenting

33. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

34. Claims 1-3, 5-6, 8-9, 18-19, 23-24, 30-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6-14, and 16 of U.S. Patent No. 6376210. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claim 1 of the instant application is directed to a method for assaying homocysteine (Hcy), S-adenosylhomocysteine (SAH) or adenosine in a sample with a mutant SAH hydrolase, wherein said mutant SAH hydrolase has binding affinity for Hcy, SAH or adenosine but has attenuated 3'-oxidative activity, 5'-hydrolytic activity, and 3' reduction activity, and wherein said attenuated activities are caused

by a mutation in the hydrolase's catalytic site, binding site for NAD, NADH, Hcy, SAH, adenosine, or a combination thereof. Claim 2 of the instant application is directed to the method of claim 1 wherein the mutation is (1) at a residue which is essential for 3'-oxidative activity, 5'-hydrolytic activity, and 3' reduction activity, or essential for binding with NADH, NAD, Hcy, SAH, or adenosine, (2) at a residue whose absence may reduce or increase 3'-oxidative activity, 5'-hydrolytic activity, and 3' reduction activity, or may reduce or increase binding with NADH, NAD, Hcy, SAH, or adenosine, or (3) at a residue adjacent to any of the residues of (1) or (2).

Claim 3 of the instant application is directed to the method of claim 1 with the added limitation that the mutant SAH hydrolase has enhanced binding affinity for Hcy, SAH or adenosine when compared to the wild-type SAH hydrolase. Claims 5-6 of the instant application are directed to the method of claim 1 wherein the mutant SAH hydrolase is derived from a mammalian or human SAH hydrolase. Claim 8 of the instant application is directed to the method of claim 1 with the added limitation that oxidized or conjugated Hcy in the sample is reduced prior to contact between the sample and the mutant SAH hydrolase. Claim 9 of the instant application is directed to the method of claim 1 with the added limitation that the Hcy in the sample is converted into SAH prior to contact with the mutant SAH hydrolase. Claim 18 of the instant application is directed to the method of claim 1 wherein SAH is contacted with the mutant SAH hydrolase in the presence of a labeled SAH, a derivative or an analogue thereof such that the amount of labeled SAH, SAH derivative or SAH analogue bound to the mutant SAH hydrolase inversely relates to the amount of SAH in the sample.

Claim 19 of the instant application is directed in part to the method of claim 18 with the added limitation that the labeled SAH is fluorophore labeled. Claim 23 of the instant application is directed to the method of claim 1 with the added limitation that the mutant SAH hydrolase is labeled. Claim 24 of the instant application is directed in part to the method of claim 23 with the added limitation that the mutant SAH hydrolase is fluorophore or enzyme labeled. Claim 30 of the instant application is directed

to the method of claim 1 with the added limitation that the mutant SAH hydrolase is immobilized. Claims 31-33 of the instant application are directed to the method of claim 1 wherein the sample is a body fluid or a biological tissue, including blood and other fluids such as urine, saliva, etc. Claim 34 of the instant application is directed to the method of claim 33 wherein the blood is separated into plasma or serum fractions.

Claim 1 of U.S. Patent No. 6376210 is directed to a method for assaying homocysteine, S-adenosylhomocysteine, or adenosine with a mutant SAH hydrolase, wherein said hydrolase comprises the amino acid sequence set forth in SEQ ID NO: 1 (identical to SEQ ID NO: 1 of the instant application) and comprises any of the following mutations: F302S, K186A, H301D, R343A, D190A, F82A, T157L, N181D, the double mutation R431A and K426R, and/or a deletion at position 432. Since SEQ ID NO: 1 corresponds to a human SAH hydrolase, it anticipates claims 1-3, 5 and 6 of the instant application as written. Claim 2 of U.S. Patent No. 6376210 is directed to the method of claim 1 as indicated above with the added limitation that the oxidized or conjugated Hcy in the sample is reduced prior to contact between the sample and the mutant SAH hydrolase. As such, it anticipates claim 8 of the instant application as written.

Claim 3 of U.S. Patent No. 6376210 is directed to the method of claim 1 as indicated above with the added limitation that the Hcy in the sample is converted into SAH prior to contact with the SAH hydrolase, therefore anticipating claim 9 of the instant application as written. Claim 6 of U.S. Patent No. 6376210 is directed to the method of claim 1 wherein SAH is contacted with the mutant SAH hydrolase in the presence of a labeled SAH, a derivative or an analogue thereof, such that the amount of labeled SAH bound to the mutant SAH hydrolase inversely relates to the amount of SAH in the sample, therefore anticipating claim 18 of the instant application as written.

Claim 7 of U.S. Patent No. 6376210 is directed to the method of claim 6 with the added limitation that the labeled SAH is fluorophore labeled. As such, it anticipates claim 19 of the instant application as

written. Claim 8 of U.S. Patent No. 6376210 is directed to the method of claim 1 wherein the mutant SAH hydrolase is a labeled mutant SAH hydrolase, therefore anticipating claim 23 of the instant application as written. Claim 9 of U.S. Patent No. 6376210 is directed to the method of claim 8 with the added limitation that the mutant SAH hydrolase is fluorophore or enzyme labeled, therefore anticipating claim 24 of the instant application as written.

Claims 10-12 of U.S. Patent No. 6376210 are directed to the method of claim 1 with the added limitation that the sample is a body fluid or a biological tissue, including blood and many other fluids such as urine, saliva, etc. Claim 13 of U.S. Patent No. 6376210 is directed to the method of claim 12 wherein the blood is separated into plasma or serum fractions. Claim 14 of U.S. Patent No. 6376210 is directed to the method of claim 10 wherein the biological tissue can be connective tissue, epithelium tissue, etc. As such, claims 10-14 of U.S. Patent No. 6376210 anticipate claims 31-33 of the instant application as written. Claim 16 of U.S. Patent No. 6376210 is directed to the method of claim 1 wherein the mutant hydrolase is immobilized, therefore anticipating claim 30 of the instant application as written.

35. Applicants are advised that claim 7 has not been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6376210 in view of the claim's interpretation as indicated above under Claim Objections, i.e. a method for assaying homocysteine, S-adenosylhomocysteine, or adenosine with a mutant SAH hydrolase, wherein said hydrolase comprises the amino acid sequence set forth in SEQ ID NO: 1 except that the threonine residue at position 158 has been substituted with a tyrosine residue. Applicants are reminded that claim 7 still recites mutants N181D and D190A, which are also recited in claim 1 of U.S. Patent No. 6376210. A double patenting rejection would be applied to claim 7 if not amended in response to this Office Action.

Conclusion

36. No claim is in condition for allowance.

37. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The Examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
January 29, 2004

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